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Research Paper

Tissue Effects in a Randomized Controlled Trial of Short-term Finasteride in Early Prostate Cancer☆

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ABSTRACT

Background: In the Prostate Cancer Prevention Trial, finasteride selectively suppressed low-grade prostate cancer and significantly reduced the incidence of prostate cancer in men treated with finasteride compared with placebo. However, an apparent increase in high-grade disease was also observed among men randomized to finasteride. We aimed to determine why and hypothesized that there is a grade-dependent response to finasteride.

Methods: From 2007 to 2012, we randomized dynamically by intranet-accessible software 183 men with localized prostate cancer to receive 5 mg finasteride or placebo daily in a double-blind study during the 4–6 weeks preceding prostatectomy. As the primary end point, the expression of a predefined molecular signature (ERβ, UBE2C, SRD5A2, and VEGF) differentiating high- and low-grade tumors in Gleason grade (GG) 3 areas of finasteride-exposed tumors from those in GG3 areas of placebo-exposed tumors, adjusted for Gleason score (GS) at prostatectomy, was compared. We also determined androgen receptor (AR) levels, Ki-67, and cleaved caspase 3 to evaluate the effects of finasteride on the expression of its downstream target, cell proliferation, and apoptosis, respectively. The expression of these markers was also compared across grades between and within treatment groups. Logistic regression was used to assess the expression of markers.

Findings: We found that the predetermined molecular signature did not distinguish GG3 from GG4 areas in the placebo group. However, AR expression was significantly lower in the GG4 areas of the finasteride group than in those of the placebo group. Within the finasteride group, AR expression was also lower in GG4 than in GG3 areas, but not significantly. Expression of cleaved caspase 3 was significantly increased in both GG3 and GG4 areas in the finasteride group compared to the placebo group, although it was lower in GG4 than in GG3 areas in both groups.

Abbreviations: GG, Gleason grade; AR, androgen receptor; PCPT, Prostate Cancer Prevention Trial; REDUCE, Reduction by Dutasteride of Prostate Cancer Events; REDEEM, Reduction by Dutasteride of Clinical Progression Events in Expectant Management; DHT, dihydrotestosterone; CRFs, case report forms; DCP, Division of Cancer Prevention; HE, hematoxylin and eosin; ERβ, estrogen receptor β; UBE2C, ubiquitin-conjugating enzyme E2C; SRD5A2, 3-oxo-5α-steroid 4-dehydrogenase 2; VEGF, vascular epithelial growth factor; GS, Gleason score; PZ, peripheral zone; TZ, transition zone; CZ, central zone.

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Interpretation: We showed that finasteride's effect on apoptosis and AR expression is tumor grade dependent after short-term intervention. This may explain finasteride's selective suppression of low-grade tumors observed in the PCPT.

1. Introduction

Progress in understanding the biology of advanced prostate cancer prompted development of therapy for castration-resistant disease; however, no parallel advances have brought improvement to prevention or treatment of early prostate cancer. This limitation, reflected in the difficulty in interpreting findings of the Prostate Cancer Prevention Trial (PCPT) (Thompson et al., 2003) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial (Andriole et al., 2010), led to denial of approval of 5α-reductase inhibitors as prostate cancer preventatives, despite their striking reduction of low-grade cancers. In both studies, the 5α-reductase inhibitors reduced the frequency of low-grade cancers but not potentially lethal high-grade cancers, pointing to the urgent need to elucidate the biologic significance.

Androgen signaling is central to prostate cancer development and progression. A milestone in progression of advanced prostate cancer when it transitions from endocrine-driven to paracrine- or intracrine-driven androgen signaling, with progressive complexities in steroid hormone biosynthesis and alterations of the androgen receptor (AR) (Logothetis et al., 2013). The PCPT, the first study to demonstrate that prostate cancer could be prevented or greatly delayed (Thompson et al., 2003), showed that men taking the type 2 5α-reductase steroid inhibitor finasteride had a relative reduction of 24.8% ($P < 0.001$) in the 7-year period prevalence of prostate cancer compared with men taking the placebo, a reduction that increased to 30% on assessment of all men who were randomized (Thompson et al., 2013). Paradoxically, incidence of high-grade disease also significantly increased among men on finasteride. Although detection bias appeared, in part, to account for the increase in high-grade disease (Lucia et al., 2007), true induction of de novo high-grade disease could not be ruled out and, therefore, the drug was not granted FDA approval for prostate cancer risk reduction.

The controversy notwithstanding, the PCPT's relevance was made clear in the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial (Fleshner et al., 2012). In that study, 302 men with low-grade prostate cancer undergoing active surveillance received three years of treatment with dutasteride or placebo. Dutasteride was associated with a 38% decrease in the cancer detection rate on repeat biopsy at year 3 (Fleshner et al., 2012), supporting the hypothesis that, based on response to a 5α-reductase steroid inhibitor, localized prostate cancer could be dichotomized as either dependent on dihydrotestosterone (DHT) or as able to adapt to DHT depletion.

To improve biologic understanding of the grade effects of finasteride, we undertook a randomized controlled trial of short-term finasteride exposure in men with clinically organ-confined prostate cancer who were scheduled for prostatectomy. We hypothesized that, following a short course of finasteride and preceding detectable morphologic changes, molecular changes associated with high-grade disease would be apparent.

2. Materials and Methods

2.1. Study Design

We performed a randomized, double-blind, placebo-controlled parallel trial comparing the tissue effects of 5-mg finasteride with those of matching placebo given orally daily 4–6 weeks before prostatectomy in patients with clinically organ-confined prostate cancer allocated 1:1 to each group at four academic medical centers. This study is a window-of-opportunity trial, which takes advantage of the interval between a clinic visit and admission to the hospital for prostatectomy, for short-term exposure to the study drug. Approved by the institutional review boards of participating sites and the National Cancer Institute Division of Cancer Prevention (DCP) Protocol and Safety Review Committee, the study was led by The University of Texas MD Anderson Cancer Center Phase I/Phase II Chemoprevention Trials Consortium in Houston. After a review of the purpose, risks, and benefits of the study, all participants signed and received a copy of a written consent. The lead organization's institutional review board provided oversight. Other participating academic centers were Cleveland Clinic in Cleveland, Ohio, The University of Texas Southwestern Medical School in Dallas, and The University of Texas Health Science Center at San Antonio. All sites collected data using protocol-specific case report forms (CRFs), which were developed from the standard set of DCP Chemoprevention CRF templates utilizing the National Cancer Institute – approved Common Data Elements. Also, all sites reported clinical data using the DCP Oracle clinical remote data capture Web-based application managed by DCP's monitoring contractor (see detailed study information at: https://clinicaltrials.gov/ct2/show/NCT00438464?term=finasteride&rank=8).

2.2. Study Participants

The Pocock-Simon Minimization Method (Pocock & Simon, 1975), a dynamic randomization method, was used to randomize patients and stratify them by biopsy GS (6 versus 7), type of prostatectomy (open vs. laparoscopic/robotic), and study site. Developed at the lead organization and available by intranet, a software program organized the randomization of participants and the dispensing of the study drug at the initial clinical evaluation. Neither patients nor medical staff members were aware of assignment, and placebo and finasteride pills were matched in appearance.

Eligible patients had histologic proof of clinically organ-confined adenocarcinoma of the prostate, clinical stage T1c or T2 disease with GS 6(3 + 3) or 7(3 + 4) or 7(4 + 3), and a prostate-specific antigen (PSA) value <10 ng/mL before registration. Participants agreed while on study not to take dehydroepiandrosterone, phytoestrogen supplements, antiandrogen therapy, saw palmetto, or dutasteride or finasteride pills independent of those provided by the study. They also had to have an Eastern Cooperative Oncology Group performance status of ≤2, be scheduled for prostatectomy in 4–6 weeks, and agree to use adequate contraception before and throughout the study. Exclusion criteria included active malignancy at any other site; prior radiation therapy for the primary tumor; history of allergic reactions attributed to compounds of chemical or biologic composition similar to that of finasteride; uncontrolled intercurrent illness; use of anticoagulation agents, except for cardioprotective doses of aspirin; use of all hormonal agents, including testosterone, saw palmetto, dutasteride, or finasteride six months before study entry (see detailed study information at: https://clinicaltrials.gov/ct2/show/NCT00438464?term=finasteride&rank=8).

Primary and secondary end points were prespecified and were assessed after prostatectomy. The primary end point was to compare the frequency of the expression of the predetermined molecular signature (ERβ, UBE2C, SRD5A2, and VEGF) differentiating high- and low-grade tumors in the GG3 areas of the two study groups, adjusted for GS at prostatectomy. The secondary end points were to compare the